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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,456	PAULSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5, 21-22, 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,21,22 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-21-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 21-22, 59-61 are currently pending and at issue in this application. Examiner regrets the inadvertent error by not including claim 5 in the elected group. Claim 5 is now included in the elected group IV.

Election/Restriction

Applicant's election with traverse of Group IV, original claims 1-5, 10, 21-22 and 59 in Paper filed on 7-19-04 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups IV and XII would not be undue burden to the Examiner. This is not found persuasive because while the searches for the two groups overlap, they are not coextensive. Furthermore, as explained in the previous Office action, the methods involve different steps and applicants have specifically call the method of group XII as "in vitro" method. (Examiner would be willing to include group XII along with group IV only if applicants acknowledge on record that any reference used to reject claims of group IV would also apply (either anticipate or render obvious) to the invention of group XII and that the two groups are obvious variations of one another).

The requirement is still deemed proper and is therefore made FINAL.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application that has matured in to a US patent. Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Examiner notes that the parent application 09/007,741 was filed with a single amino acid sequence. However, the current divisional application lacks such sequence information. Applicants are urged to either file a request for transfer of sequence information from parent to the divisional or separately file the sequence information.

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that on page 3, applicants recite an amino acid sequence without any SEQ ID NO. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the phrase "which substantially lacks a membrane spanning domain". The metes and bounds of the above phrase especially the word "substantially" in the context of the above claim is not clear to the Examiner. Correction is required.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is drawn to a method where in the enzyme used has "an amino acid sequence that is at least 40% identical to a sialyl motif of an ST3Gal I sialyltransferase". However it is not clear to the Examiner whether such an enzyme will continue to have the specific functional properties of ST3Gal I. A quick perusal of the specification did not provide any ample explanation for the above limitation in the claim.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 is drawn to a method wherein the sialyltransferase (i.e., ST3GalI) is produced by "recombinant expression of a sialyltransferase in a host cell". While the intent of the applicant is clear to the Examiner, the claim as written does not specifically indicate that the recombinantly expressed enzyme is indeed the ST3GalI and appears to indicate that it could be any sialyltransferase. Examiner suggests amending the claim to indicate that the expressed enzyme is indeed ST3GalI.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 59 recites the phrase "a greater percentage of terminal galactose residues are sialylated…". The metes and bounds of the above phrase specifically the word "greater" in the context of the above claim is not clear to the Examiner.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sialylating a saccharide group on a recombinant glycoprotein, comprising contacting a saccharide group which comprises a galactose or N-acetylgalactosamine acceptor moiety on a recombinant glycoprotein with a sialic acid donor moiety and a recombinant ST3Ga1 1 sialyltransferase in a reaction mixture which provides reactants required for sialyltransferase activity for a sufficient time and under appropriate conditions to transfer sialic acid from said sialic acid donor moiety to said saccharide group, wherein the sialic acid donor is *in situ* generated CMP-sialic acid and the recombinant enzyme lacks the membrane spanning domain, does not reasonably provide enablement for such a method wherein the recombinant ST3GalI enzyme includes a sialyl motif which has an amino acid sequence that is at least about 40% identical to a sialyl motif from an ST3Ga1 1 sialyltransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention (i.e., recombinant ST3GalI enzyme having a sialyl motif which has an amino acid sequence that is at least about 40% identical to a sialyl motif from an ST3Ga1 1 sialyltransferase) commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 5 is so broad as to encompass a method of sialylating a saccharide group using any sialyltransferase which has an amino acid sequence that is at least about 40% identical to a sialyl motif from an ST3Gal 1 sialyltransferase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sialyltransferases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of using just ST3Gal I sialyltransferase only. It would require undue experimentation of the skilled artisan to make and use the sialyltransferase which has an amino acid sequence that is at least about 40% identical to a sialyl motif from an ST3Gal 1 sialyltransferase. The specification is limited to teaching the use of ST3Gal I in the above method but provides no guidance with regard to the making of variants and mutants of ST3Gal I. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue

experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the variant polypeptides encompassed by this claim for the use in the claimed method.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses the use of any variant sialyltransferase which has an amino acid sequence that is at least about 40% identical to a sialyl motif from an ST3Gal 1 sialyltransferase because the specification does not establish: (A) regions of the protein structure which may be modified such that it would not affect the specific ST3Gal I activity; (B) the general tolerance of sialyltransferases to modification and extent of such tolerance such that it would result in ST3Gal I activity; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the variant enzyme in the claimed method in a manner reasonably correlated with the scope of the claims broadly including variant sialyltransferases with an

enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variant sialyltransferases having the desired biological characteristics for use n the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5, 21, 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (Glycoconjugate J., 1995, Vol 12:755-761). This rejection is based upon the public availability of a printed publication. Claims 1-2, 5, 21, 59-61 of the instant application are drawn to a method of sialylating a saccharide group comprising a galactose or a N-acetylgalactosamine acceptor moiety or a recombinant glycoprotein with a sialic acid donor moiety and a recombinant ST3Gal I sialyltransferase in a reaction mixture required for sialyltransferase activity for a sufficient time and conditions for transfer of sialic acid from said sialic acid donor moiety to said saccharide moiety, wherein the sialic acid donor moiety is CMP-sialic acid, wherein a greater percentage (at least 80-90%) of the terminal saccharide residues

are sialylated. Williams et al. disclose an identical method of sialylation of a glycoprotein using recombinant ST3Gal I sialyltransferase enzymes, wherein the sialic acid moiety is CMP-NANA and wherein at least 80-90% of the terminal saccharide get sialylated (see the entire document especially see page 757 columns 1 and 2). Thus Williams et al. anticipate claims 1-2, 5, 21, 59-61 of this application as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-4, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. as applied to claims 1-3, 5, 21, 59-61 above, and further in view of Wong et al. (US 5,374,541 dated 12-20-1994) and Kurosawa et al. (Biochim Biophys Acta, 1995, Vol. 1244(1):216-222) and Paulson et al. (US 5,541,083, dated 7-30-96). Claims 3, 22 in this instant application is drawn to a method of sialylating a saccharide group comprising a galactose or a N-acetylgalactosamine acceptor moiety or a recombinant glycoprotein with a sialic acid donor moiety and a recombinant sialyltransferase (ST) such as ST3Gal I, in a reaction mixture required for ST activity for a sufficient time and conditions for transfer of sialic acid from said sialic acid donor moiety to said saccharide moiety, wherein the sialic acid donor moiety is CMP-sialic acid, wherein the sialic acid is NeuAc is regenerated *in situ* , wherein the recombinant ST is a

eukaryotic ST substantially lacking a membrane-spanning domain and comprising a sialyl motif which has an amino acid sequence that is at least about 40% identical to sialyl motif of a natural ST, produced by a recombinant expression of a cDNA clone in a host cell such as a fungus *A.niger*.

Williams et al. teach an *in vitro* method of sialylating a glycoprotein (discussed above). However, the reference does not teach a recombinant ST lacking a membrane spanning domain or the regeneration of CMP-NANA *in situ* in the reaction mixture. The reference also does not teach the use of host cells such as a fungus.

Wong et al. teach a method of *in situ* regeneration of CMP-sialic acid for a one pot synthesis of oligosaccharides. They demonstrate the *in situ* regeneration of CMP-sialic acid such as NeuAc that sialylates formed galactosyl glycoside in the presence of a ST.

Kurosawa et al. teach or provide a recombinant clone for ST3Gal I enzyme which can be used in the above method. Paulson et al. teach a recombinant method for production of ST which lack both a membrane-spanning domain and a retention signal in order to increase the secretion of the recombinant enzymes using several types of host cells including fungi such as *A.niger* which can be used for making recombinant enzyme as provided by Kurosawa et al.

Combining the teachings of all the above references it would have been obvious to one skilled in the art at the time the invention was made to develop a large-scale or commercial scale method of sialylation of a glycoprotein under conditions using large amounts of recombinant ST enzymes. Using the clone provided by Kurosawa et al. and the recombinant technique provide by Paulson et al. it would have been obvious for one skilled in the art to make large amounts of recombinant ST enzyme lacking membrane-spanning domain so that the recombinant enzyme

would be liberated out of the cell in any eukaryotic host cell such as an insect cell line, a mammalian cell line, or a fungal cell including *A.niger* which is a commonly used host cell for production of several recombinant enzymes. Using such recombinant ST and the teachings of Wong et al. along with teachings of Williams et al. it would have been obvious to one skilled in the art to develop a commercial scale method of sialylation with *in situ* regeneration of CMP-sialic acid. In order to achieve maximum sialylation, it would have been obvious for one skilled in the art to vary the concentrations of the enzymes, reaction conditions in terms of donor and acceptor concentrations and the number of enzymes in the reaction mix to get various percentages of sialylation such as 80-90% and various terminal groups.

One would be motivated to do this in order to study the mechanism of action of ST3Gal I. As the yield of these membrane bound enzymes are very poor during recombinant method of making, Paulson et al. teach that one skilled in the art would be motivated to produce recombinant ST without membrane-spanning domain so that large amounts of said enzymes liberated into the culture medium could be harvested. One skilled in the art would have a reasonable expectation of success since all the above references teach reliable and time-tested methods that has been used by a number of other inventors.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 21-22, 59-61 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 10 of U.S. Patent No. 6,399,336. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-5, 21-22, 59-61 of the instant application and claims 1-5, 10 of the reference patent are both directed to large-scale or commercial scale

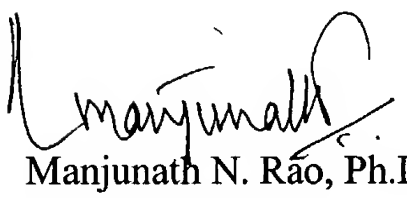
method of sialylating a saccharide group on a recombinant glycoprotein using , specifically a recombinant ST3Gal I. The method claimed in the instant application and the method encompassed in the reference patent are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the claimed method includes several embodiments that would anticipate the method claimed in claims herein. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-5, 10 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 1-5, 21-22, 59-61 of the instant application. Alternatively, claims 1-5, 21-22, 59-61 cannot be considered patentably distinct over claims 1-5, 10 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-5, 10 of that patent and falls within the scope of claims 1-5, 21-22, 59-61 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-5, 10 of the reference by selecting a specifically disclosed embodiment that supports those claims. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-5, 10 of the reference patent.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura

Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

September 25, 2004